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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,140	10/31/2005	Eva Kontsekova	SONN:065US	5448

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,140	KONTSEKOVA, EVA	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-34* is/are pending in the application.

4a) Of the above claim(s) *24-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-09-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 24-34 are presently pending. Claims 24-32 are withdrawn as being drawn to a non-elected invention.

3. Claims 33-34 are presently under examination.

Response to Arguments

Election/Restriction

4. Although the restriction requirement was made final in the prior Office Action, Applicants continued to traverse the examiner's position. Applicants continue to argue that the type IA tau molecule set forth in the instant claim 24 is not disclosed in the prior art, and therefore the holding of lack of unity of invention is improper. According to Applicants, the examiner has failed to interpret the claims in light of the specification as filed. Applicants have even provided a Declaration stating that although the primary structure of the prior art type IA tau molecule having the same sequence as SEQ ID NO: 1 of the instant application, that the type IA tau molecule set forth in the claims is conformationally distinct. However, the Declaration of Dr. Novak is ineffective since the specification as filed did not set forth this distinction, and the instant claims do not recite any particular conformation that is required to distinguish the claimed type IA tau molecules from the prior art. Instant claim 26 clearly recites that the type IA tau molecule comprises an amino acid sequence of any of SEQ ID NO: 1 to 3. There is no mention of any additional elements that would contribute some other conformational

information that is not present in another type IA molecule having the same sequence, in the instant case SEQ ID NO: 1 which is clearly disclosed in the prior art. "[A]lthough the claims are interpreted in light of the specification, limitations from the specification are not read into the claims." See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, contrary to Applicant's assertions, "[U]SPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). Limitations appearing in the specification but not recited in the claim should not be read into the claim. E-Pass Techs., Inc. v. 3Com Corp., 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) (claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily)."

5. Applicant's arguments are not sufficient to overcome the previous holding of lack of unity of invention. As stated in the prior Office Action, restriction requirement is made final.

Claim Rejections - 35 USC § 112

6. Claims 33-34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a transgenic mouse comprising a genome having a double truncated tau sequence integrated therein, does not reasonably provide enablement for making a transgenic animal of *any* species of animal, wherein the genome of said animal comprises a double truncated tau sequence integrated into the endogenous tau equivalent gene of said any species of animal, and further wherein said

animal exhibits Alzheimer's disease associated risk factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

7. Applicant's arguments filed 6-09-08 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that Example 14 discloses a method for generating transgenic animals by pronuclear injection. Moreover, Applicants have provided a declaration by Dr. Filipcik to provide evidence that a person skilled in the art is able to produce transgenic animals with predictable phenotype using gene constructs described in the present application.

8. Dr. Filipcik described several independent transgenic rat lines #318 and #72 which encode a truncated tau 43 protein of amino acids 93-333, additionally transgenic rat line #24 encodes amino acids 93-302. According to the Declaration, at ¶ #6, the phenotypes of these transgenic animals was similar, however differ in the strength of the resulting phenotype. Dr. Filipcik concludes this paragraph by stating that the aggressiveness of neurodegeneration in human tauopathies including Alzheimer's disease may also be different in different patients. Moreover, further neurological examinations showed similar features in both the #24 and #318 transgenic rat lines. Applicant's observations appear to support the examiner's position set forth in the prior Office Action, that at the effective filing date of the present application (07/12/2002), the transgenic art was and continues to be unpredictable with respect to the generation of any transgenic animal and transgene behavior *in vivo*, and that transgene expression in different species of transgenic non-human animals is not predictable and varies

according to the particular host species, specific promoter/gene combinations, random transgene insertion and genetic imprinting (e.g., transcriptional silencing of a gene based on transmission from parent to offspring of repressive nucleosomal structures) (Sanders Williams et al., J. Appl. Physiol. 2000, p. 1125, col. 1, paragraph 3 and p. 1124, col. 2, paragraph 2). If transgene expression was predictable, the ordinary skilled artisan would have expected that the phenotypes of transgenic lines #318 and #72 would have been essentially identical since the transgene constructs used to produce these transgenic lines, comprise the same form of doubly truncated tau protein. Instead, Applicants observed more similarities between #318 and transgenic line #24, which were produced by constructs expressing different forms of doubly truncated forms of tau protein. Moreover, Applicants concluded that all transgenic lines exhibited some form of neurofibrillary pathology, which according to Applicants is the most important earliest immunohistochemical finding in Alzheimer's disease. However, contrary to Applicant's assertions, there is no indication that the neurofibrillary pathologies observed by Applicants in the transgenic lines are necessarily indicative of a single neurodegenerative disorder, since it is known in the art that neurofibrillary tangles are associated with widely divergent neurodegenerative diseases in terms of their pathologic mechanisms, such as disorders including supranuclear palsy, parkinsonism linked to chromosome 17, corticobasal degeneration, and others (See Gotz 2001, Abstract).

9. Moreover, Applicants do not provide any specific information regarding the tissue specific promoters used in their experiments to provide specific expression of the doubly

truncated tau proteins used to produce the rat transgenic lines having a neurofibrillary phenotype as set forth in the Declaration. Since the instant claims are not limited to any particular non-human animal, any specific form of doubly truncated tau transgene that expresses a specific conformationally restricted epitope of tau protein in a tissue specific manner to produce the neurofibrillary phenotype, and other phenotypes (such as *spontaneous hypertension, dys-lipidaemia or diabetes*) associated with Alzheimer's disease, the ordinary skilled artisan would have to undergo undue experimentation for one skilled in the art to produce the full scope of transgenic organisms encompassed by the instant claims.

10. The scope of potential forms of doubly truncated tau molecules expressed in the claimed non-human transgenic animals is tremendous, and the exact nature of the possible phenotypes produced by the plurality of potential transgenes expressing the claimed truncated tau molecules cannot be predicted and must be determined *de novo* for each individual form of transgene.

11. Furthermore, since the guidance provided in the Declaration to produce the transgenic lines #318 and #24 was not explicitly set forth in the specification as filed, Applicants cannot rely upon post filing data to provide evidence that the ordinary skilled artisan using the specification as filed would have been able to practice the full scope of the claimed invention without undue experimentation.

12. See, MPEP 2164.05, which states: "[T]o overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art

at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention."

The instant specification fails to teach which specific amino acids to be substituted, deleted or inserted within the minimally truncated tau core, at which positions and in which combinations such that the encoded polypeptide derivative for N- and C-terminally truncated tau gene is still functional to yield results contemplated by Applicant. The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein one specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Similarly, in discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study (Page 6, Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). Post filing art teaches that even single-nucleotide

polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). Though the recombinant technology for the generation of new mutant proteins is highly developed, the ability to determine *a priori* whether a mutation and/or deletion and/or insertion will generate a functional protein is not predictable. Since the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, it would require undue experimentation for one skilled in the art to determine alternative sequences of N- and C-terminally truncated tau protein molecules, such that transgenic animal expressing this truncated protein would produce an animal model suitable for isolating therapeutic candidates for the treatment of Alzheimer's disease.

In so far as the expression of a transgene, it was also well known in the art at the time of filing that expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter that controls gene expression (Kappel, Current Biology, 1992, entire document, specifically, p. 349, col. 2 paragraph 1). Additionally, it was well known in the art that not all promoters result in efficient expression or expression at levels in the appropriate tissues to result in a phenotype that is useful (Williams et al., (J. Appl. Physiol., 2000, p. 1124, col.2, lines 15-19). Logan et al., (1999, Clinical and Experimental Pharmacology and Physiology, p. 1021, col. 2, paragraph 2) further corroborates that the challenge in the development of transgenic animals in not in the process, but the design of the construct that will allow for the expression of the gene of interest in the desired cell type at an appropriate level.

Therefore, it is clearly set forth in the art that for effective expression of a gene of interest in tissue specific manner, it is necessary to link the gene of interest to the appropriate tissue specific promoters. Thus, since Applicant's have not provided the appropriate guidance in this regard, the skilled artisan would have to resort to de novo experimentation to practice the full scope of the claimed invention.

Due to the breadth of the claimed invention, the limited and prophetic guidance in the specification as filed, and the unpredictability associated with the production of a transgenic animal exhibiting a phenotype that correlates with risks factors associated with Alzheimer's disease, the skilled artisan would have to undertake undue experimentation to practice the full scope of the claimed invention.

Double Patenting

13. Claims 33-34 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-21 of copending Application No. 10/521049. According to Applicants, a terminal disclaimer will be filed if the copending application issues as a US Patent. Also, Applicants stated that if the obvious type double patenting rejection remains as the only rejection of record, the examiner should withdraw the rejection.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE